Gut microbiota and osteoarthritis management: an expert consensus of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)

Emmanuel Biver[1], Francis Berenbaum[2], Ana M. Valdes[3], Islene Araujo de Carvalho[4], Laure B. Bindels[5], Maria Luisa Brandi[6], Philip C. Calder[7, 8], Vincenzo Castronovo[9], Etienne Cavalier[10], Antonio Cherubini[11], Cyrus Cooper[8, 12, 13], Elaine Dennison[12], Claudio Franceschi[14], Nicholas Fuggle[12], Andrea Laslop[15], Pierre Miossec[16], Thierry Thomas[17], Sansin Tuzun[18], Nicola Veronese[19], Mila Vlaskovska[20], Jean-Yves Reginster[21, 22], René Rizzoli[1]

1 Division of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland

2 Sorbonne Université, INSERM CRSA, Department of Rheumatology, AP-HP Saint-Antoine Hospital, Paris, France.

3 Division of Rheumatology, Orthopaedics and Dermatology, School of Medicine, University of Nottingham, Nottingham, UK

4 Department of Ageing and Life Course, World Health Organization, 20 Avenue Appia, 1211, Geneva 27, Switzerland.

5 Louvain Drug Research Institute, Metabolism and Nutrition Research Group, Université Catholique de Louvain, Brussels, Belgium

6 Bone Metabolic Diseases Unit, Department of Biomedical, Experimental and Clinical Sciences, University of Florence, Florence, Italy.

7 Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK

8 NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, UK

9 Metastases Research Laboratory, GIGA-Cancer, University of Liege, Liege, Belgium

10 Department of Clinical Chemistry, University of Liege, CHU de Liège, Liège, Belgium

11 Geriatria, Accettazione geriatrica e Centro di ricerca per l'invecchiamento. IRCCS INRCA, Ancona, Italy

12 MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

13 NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK

14 Department of Specialty, Diagnostic and Experimental Medicine (DIMES), University of Bologna, Bologna, Italy

15 Scientific Office, Austrian Medicines & Medical Devices Agency, Federal Office for Safety in Health Care, Vienna, Austria

16 Immunogenomics and Inflammation Research Unit, EA 4130, University of Lyon, and Department of Clinical Immunology and Rheumatology, Hospices Civils de Lyon, Lyon, France

17 Department of Rheumatology, Hôpital Nord, CHU de Saint-Etienne, and INSERM U1059, University of Lyon, Saint-Etienne, France

18 Department of Physical Medicine and Rehabilitation, Cerrahpaşa Medical Faculty, Istanbul University Cerrahpaşa, Istanbul, Turkey

19 National Research Council, Neuroscience Institute, Aging Branch, Padova, Italy.

20 Medical Faculty, Department of Pharmacology, Medical University Sofia, Sofia, Bulgaria.

21 Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium

22 Chair for Biomarkers of Chronic Diseases, Biochemistry Department, College of Science, King Saud University, Riyadh, KSA

Correspondence to: Emmanuel Biver, Division of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, University of Geneva, 4 Rue Gabrielle Perret-Gentil, 1205 Geneva, Switzerland. Tel: +41 22 382 99 50. Fax: +41 22 382 99 75. E-mail: Emmanuel.Biver@hcuge.ch

Conflict of interest

AMV is consultant for Zoe Global Ltd, CPKelco Inc and Heel GmbH; The others authors have no conflict of interest to declare relevant to the content of this review.

Abstract

The prevalence of osteoarthritis (OA) increases not only because of longer life expectancy but also because of the modern lifestyle, in particular physical inactivity and diets low in fiber and rich in sugar and saturated fats, which promote chronic low-grade inflammation and obesity. Adverse alterations of the gut microbiota (GMB) composition, called microbial dysbiosis, may favor metabolic syndrome and inflammaging, two important components of OA onset and evolution. Considering the burden of OA and the need to define preventive and therapeutic interventions targeting the modifiable components of OA, an expert working group was convened by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) to review the potential contribution of GMB to OA. Such a contribution is supported by observational or dietary intervention studies in animal models of OA and in humans. In addition, several well-recognized risk factors of OA interact with GMB. Lastly, GMB is a critical determinant of drug metabolism and bioavailability and may influence the response to OA medications. Further research targeting GMB or its metabolites is needed to move the field of OA from symptomatic management to individualized interventions targeting its pathogenesis.

Keywords:

- Osteoarthritis
- Gut microbiota
- Dysbiosis
- Inflammaging
- Obesity
- Modern diet

1. Introduction

Osteoarthritis (OA) is one of the most common musculoskeletal diseases, and its prevalence is rising, particularly since the mid-20th century. In addition, the burden of musculoskeletal diseases increases and is particularly high in Europe (Sebbag et al., 2019). A recent report of the Global Burden of Diseases, Injuries, and Risk Factors Study 2015 identified OA as the non-communicable disease associated with the most notable increase of total burden and age-standardized disability-adjusted life-years (DALY) rates (+35% and + 4% between 1990 and 2015, respectively) (GBD 2015 DALYs and HALE Collaborators, 2016). The increased longevity of the most recent generations cannot solely explain this epidemiological observation (Wallace et al., 2017). Some authors suggest that OA might be considered as a mismatch disease, meaning that OA would be more common today than in the past because genes inherited from previous generations are inadequately or imperfectly adapted to modern environmental conditions (Berenbaum et al., 2018). Therefore, at any given age, the prevalence of OA might be higher in modern environments because of higher levels of obesity and chronic metabolic inflammation (metaflammation) favored by physical inactivity, and low-fiber diets with great amounts of processed foods that are rich in sugar and saturated fats. If so, the classical phenotypic approach to OA based on the known risk factors (age, obesity, trauma) and on imaging will likely result in important components of OA pathophysiology being missed, in particular modifiable environmental factors which might be targeted with interventions aimed at improving the development and burden of the disease (Berenbaum, 2019).

In this context, several sources of data support that microbial dysbiosis, corresponding to an adverse alteration of gut microbiota (GMB) composition and function, is causative of metabolic syndrome and is associated with low-grade inflammation, which are important components of the onset of musculoskeletal diseases. In addition, specific dietary

interventions may control low-grade inflammation (Calder et al., 2017; Sanna et al., 2019). To what extent GMB might represent the missing link between metabolic changes associated with modern environmental conditions and OA pathogenesis and manifestations remains however unclear. Considering the burden of OA and the need to define preventive and therapeutic interventions targeting the modifiable components of OA pathophysiology, a working group was convened by the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) to review the potential contribution of GMB to OA. Three main aspects emerged from the review of the topic: first, GMB interacts with many well-recognized risk factors of OA. Second, some observational or intervention studies support the contribution of GMB to OA. Last, interactions between medications and GMB need to be taken into account in OA management.

2. GMB interactions with risk factors of OA

Several risk factors acting together contribute to a complex interplay between mechanical, cellular and biochemical factors leading to the pathogenesis of OA and the individual susceptibility to OA (Figure 1) (Hunter and Bierma-Zeinstra, 2019). Local abnormal loading of joints increases the risk of developing OA. However, non-mechanical factors at the patient level are also involved in this process (Berenbaum, 2013). It is now clearly established that OA is a low-grade inflammatory condition and that systemic inflammation contributes to the development of OA, and enhances its symptomatic expression, particularly impaired function and pain (Jin et al., 2015). Important contributors to chronic low-grade inflammation are represented by obesity, metabolic syndrome and a diet rich in saturated fats; the role of the GMB appears to be the missing link between these conditions and OA.

2.1. Age and inflammation

The prevalence of OA increases with age. Age-related differences in the GMB composition have been described among young adults, older adults, and centenarians (Claesson et al., 2011; O'Toole and Jeffery, 2015). In particular, specific alterations of GMB composition were observed in centenarians, notably an increase of opportunistic proinflammatory bacteria generally present in the adult gut ecosystem in low numbers (facultative anaerobes, notably pathobionts), and a marked decrease in symbiotic species with reported anti-inflammatory properties (clostridial clusters such as *Faecalibacterium prauznitzii* and relatives) (Santoro et al., 2018). These modifications have been associated with systemic inflammation, since strong correlations exist between plasma levels of pro-inflammatory cytokines, such as IL-6 and IL-8, and the enrichment in bacteria belonging to Proteobacteria phylum or the decrease in the amount of bacteria belonging to Firmicutes phylum (butyrate-producing bacteria, in particular clostridial clusters) (Biagi et al., 2010). These anti-inflammatory effects may be due, at least partly, to the secretion by these bacteria of anti-inflammatory peptides belonging to a protein called Microbial Anti-inflammatory Molecule (MAM), or other metabolites, able to block NF-kappa B activation and IL-8 production (Quevrain et al., 2016; Sokol et al., 2008). These data suggest that the intestinal ecosystem in older subjects contributes to inflammaging (Franceschi et al., 2018). Part of this phenomenon can be assumed to be linked to the aging process, regardless of life-style and dietary habits, since similar patterns were observed in Europe and China (Biagi et al., 2016; Wang et al., 2015). GMB functional profile analyses confirmed that the age-related changes in GMB are associated with a reduction in genes involved in pathways responsible for the production of short-chain fatty acids (SCFAs) via proteolytic fermentation, as well as an increase in bacterial genes involved in tryptophan metabolism pathways (Franceschi et al., 2017).

2.2.Sex and estrogen

Women are at higher risk of OA, and tend to have more severe OA, particularly after the menopausal age (Srikanth et al., 2005). The increase in incidence of OA at the time of menopause has led to hypotheses regarding the role of estrogens in OA. Estrogens deprivation may unmask the symptoms of OA by enhancing pain sensitivity (de Kruijf et al., 2016). The interaction of sex steroids with GMB has been nicely investigated in models of bone loss in hypogonadal mice. These models showed that estrogen deficiency induces the loss of intestine barrier function, leading to endotoxemia and an increase of TNFα-expressing $CD4^+$ T cells, and bone loss (Li et al., 2016b). In contrast, hypogonadal germ-free mice maintain adequate barrier function following estrogen deficiency and do not experience such bone loss. The reintroduction of gut microbes into germ-free mice reversed the osteoprotection exerted by an absence of microbiota. In addition, sex-steroid deficiency associated bone loss is prevented by probiotics supplementation (*Lactobacillus rhamnosus GG*) (Iqbal et al., 2016; Li et al., 2016b). Taken together, these data illustrate that estrogen deficiency may contribute to inflammaging by a microbiota-dependent pathway.

2.3.Obesity

Although the strongest associations between obesity and OA are observed for weight-bearing joints, obesity also increases OA risk at non-weight-bearing regions, such as hands (Visser et al., 2015; Yusuf et al., 2010). Preclinical data support that obesity-related microbial dysbiosis drives the inflammatory process of OA pathogenesis associated with obesity. In various animal models, the severity of adiposity and systemic inflammation increases load-induced cartilage damage (Collins et al., 2015). Alterations of the GMB composition with chronic antibiotics in mice that spontaneously develop a metabolic syndrome phenotype due to alterations in functions of the gut microbiome, attenuate cartilage

damage (Guss et al., 2019). Restoring a healthy microbial community using the indigestible prebiotic fiber oligofructose in obese mice is associated with a reduction of systemic and knee joint inflammation, a preservation of articular cartilage, and a protection against OA (Schott et al., 2018). These data suggest that the GMB may contribute to the severity of load-induced OA cartilage pathology and subchondral bone morphology and support the concept of a metabolic phenotype of OA (Szychlinska et al., 2019).

The GMB might mediate OA via the translocation of microbiota-derived molecules into the systemic circulation. Lipopolysaccharide (LPS) is mainly produced by the gastrointestinal microbiota and its migration from the gut into the circulation contributes to low-grade inflammation. Metabolic endotoxemia involving interaction of gut derived-LPS and Toll-like receptor (TLR) 4 has been recently considered as a common source of low grade inflammation (Boutagy et al., 2016). The altered clearance of LPS in obesity and metabolic syndrome may contribute as well to the link between these conditions and OA (Huang and Kraus, 2016). Preclinical studies demonstrated that LPS suppresses cartilage matrix synthesis activity via an up-regulation of IL-1beta through TLRs involved in innate immunity and which are present in human articular cartilage (Bobacz et al., 2007). Based on these data, serum levels of LPS might be a useful biomarker of OA severity and progression. An association of LPS with severity of inflammation, symptoms and radiographic abnormalities of knee OA was reported in an exploratory study in 25 patients. Serum LPS levels were positively associated with the abundance of activated macrophages in the knee joint capsule and synovium, knee osteophyte severity, knee joint space narrowing severity, total WOMAC score, and self-reported knee pain score (Huang et al., 2016). LPS-binding protein (LBP) might also be an interesting alternative biomarker to detect metabolic endotoxemia associated to OA (Huang et al., 2018). These data suggest that metabolic endotoxemia, caused by impaired gut mucosal integrity and low-grade chronic inflammation observed in obese

patients, may account for the association between obesity and OA at non-weight-bearing joints which cannot be explained by biomechanical factors (Metcalfe et al., 2012). To what extent LPS-lowering interventions such as a high-fiber diet, weight loss, exercise, antibiotics or microbiota transplant, may reduce OA progression remains to be investigated.

Another observation supporting the close link between obesity-related low-grade inflammation and OA is the outcome of bariatric surgery in patients with symptomatic hip or knee OA. The massive weight loss (20%) after this surgery is associated with an improvement of pain and function which is parallel to the decrease of the low-grade inflammatory state (Gill et al., 2011; Richette et al., 2011). Concerning fat mass, adipose tissue function and signaling might be a key host response to microbial dysbiosis. In germ-free mice receiving GMB from conventionally raised animals, intestinal absorption of monosaccharides and insulin resistance increase, resulting in de novo hepatic lipogenesis and deposition of triglycerides in adipocytes (Backhed et al., 2004). Thus, GMB can be considered as an environmental factor that affects energy storage and body-fat accumulation. The circadian transcription factor NFIL3 has been identified as an essential molecular link among the GMB, the circadian clock, and host metabolism (Wang et al., 2017). Thereby, the regulation of adiposity by GMB might modulate body composition and low-grade chronic inflammation which both contribute to OA pathogenesis and symptoms.

2.4. Diet

GMB diversity and functionality are strongly modulated by the host's diet (Mills et al., 2019). Postprandial elevation of LPS in the circulation is increased by GMB dysbiosis induced by a high-fat diet. In animal models, diet-induced obesity results in an inflammatory profile promoting the development of metabolic OA (Collins et al., 2016; Collins et al., 2018). In this regard, a recent study (reported in Table 1) showed that a high-fat/high-sucrose (HFS) diet led

to development of knee joint damage in rats that was associated with changes in the metabolic profile in these animals, and that was prevented with prebiotic fiber supplementation and aerobic exercise. In these rats exposed to a HFS diet, prebiotic fiber prevented increases in serum endotoxin and microbial dysbiosis, supporting again the concept that obesity-related metabolic dysregulation and microbial dysbiosis might be strongly linked to the metabolic OA phenotype (Rios et al., 2019). In humans, data from the Framingham cohort and the Osteoarthritis Initiative found that intake of dietary fiber was inversely associated with risk of symptomatic OA (Dai et al., 2017a; Dai et al., 2017b). Further analysis suggested that the association between fiber intake and OA was only in part mediated by BMI and CRP levels (Dai et al., 2018). Another longitudinal analysis using the Osteoarthritis Initiative database showed that higher adherence to Mediterranean diet was associated with a significantly lower risk of pain worsening and symptomatic knee OA, whilst no significant effect was observed on the incidence of radiographic knee OA. The authors hypothesized that this observation might be mediated by the anti-inflammatory properties typical of a Mediterranean diet, which is particularly rich in some nutrients that may have a protective effect on OA outcomes, such as fibers and which may lower oxidative stress markers (Veronese et al., 2018). Fiber-rich diets are the main fermentable sources for SCFAs which contribute to the attenuation of systemic inflammation by inducing regulatory T cells and the control of bone remodeling (Lucas et al., 2018). SCFAs are also involved in a gut-brain axis which may contribute to pain modulation (Russo et al., 2018).

2.5 Mechanical loading and exercise

Regular physical activity, in particular non-weightbearing exercises, seems to have both preventive and therapeutic benefits for individuals with OA (Mazor et al., 2019). On the contrary, high-impact sports and regular weightbearing sports may promote OA. Beyond the

mechanical effects on cartilage and subchondral bone, the type, intensity and frequency of physical activity may modulate several metabolic pathways via interfering with the GMB. Exercise might change GMB composition, functional capacity, and metabolites, independently of diet (Monda et al., 2017). The potential mechanisms involved in response to exercise include the improvement of the Bacteroidetes-Firmicutes ratio, the modification of the profile of bile acids, the increase of SCFAs production, the reduction of LPS effects via suppression of TLR signaling, and the modification of mucosal immunity (Cerda et al., 2016). In response to intense exercise, the GMB may control the oxidative stress and inflammatory responses and improve metabolism and energy expenditure (Mach and Fuster-Botella, 2017). These effects may depend on exercise modality and intensity, and on obesity status (Mailing et al., 2019). Exercise might also be associated with specific diet pattern which may also modulate GMB or its metabolites (Jang et al., 2019). In animal models, OA induced by destabilization of the medial meniscus is reduced in germ-free mice, suggesting that microbial dysbiosis could participate to mechanical-loading induced OA (Ulici et al., 2018). To what extent interventions with exercise in synergy with different diets may rebalance microbial dysbiosis enough to impact OA symptoms or evolution remains to be investigated.

3. Studies exploring the contribution of GMB to OA

3.1.Observational studies

OA is characterized by a chronic, low-grade inflammation which is mediated primarily by the innate immune system, making it distinct from that observed in rheumatoid arthritis and other autoimmune joint diseases (Robinson et al., 2016). This concept is supported by the discovery of an increased prevalence of hand OA in obese patients, suggesting that OA in these patients is not solely the result of greater load supported by the joint cartilage and bone, and paving

the way to the hypothesis of close links between adipokines, low-grade inflammation, metabolic syndrome and OA (Berenbaum, 2013; Jiang et al., 2016; Reyes et al., 2016). The GMB is involved in many physiological functions, including mucosal barrier function, immune system regulation, food digestion (fermentation of undigested nutrients), energy metabolism, and with the production of bioactive agents such as SCFAs, estrogens, and serotonin (Lucas et al., 2018). The composition of GMB, and its adverse perturbations, may be involved in many chronic diseases known to be associated with musculoskeletal disorders, such as inflammatory bowel diseases, obesity, type 2 diabetes, auto-immune diseases, frailty, malnutrition, and cancer (Bindels et al., 2018; Steves et al., 2016). Some of these conditions are also classically recognized as risk factors of OA. While several data support the hypothesis that GMB may influence bone homeostasis (D'Amelio and Sassi, 2018; Rizzoli, 2019), recent observational studies suggest that GMB may also be associated with OA. A large cross-sectional analysis of a population based cohort in UK found that OA was associated with a large number of GMB features (Jackson et al., 2018). In particular, the abundance of specific gut microbes (*Lentispherea*) was negatively associated with prevalence of OA and rheumatoid arthritis (Jackson et al., 2018). In addition, the presence of bacterial nucleic acids has been identified in synovial fluid and tissue samples of OA lesions. These bacterial nucleic acids were different from those found in samples from patients with rheumatoid arthritis (Zhao et al., 2018). Taken together, these data support the concept that GMB may influence joint biology.

3.2. Intervention studies

Table 1 summarizes controlled interventional studies investigating whether specific microbes, fermentable fibers and/or bacterial metabolites influence OA. Very few studies have explored this topic; those that have been conducted have been of short duration (≤ 6 months) and

include only one study in humans. In this study of 537 patients with knee OA, daily supplementation with probiotic *Lactobacillus casei shirota* over 6 months significantly improved functional scale (WOMAC) and pain (visual analog scale), and lowered systemic inflammation (C-Reactive Protein) compared to placebo (Lei et al., 2017). All other studies were performed in animal models of chemical or trauma-induced, or spontaneous OA, including some studies in obese animals. Intervention consisted of supplementation with either probiotics (Korotkyi et al., 2019; Kwon et al., 2018; So et al., 2011), prebiotics (Rios, 2019; Rios et al., 2019; Schott et al., 2018) or butyrate (Sim et al., 2018), a SCFA produced by the GMB involved in many metabolic processes. Compared to their respective controls, these interventions decreased the histological changes associated with OA and also modified systemic inflammation profiles. Interestingly, in the two studies using diet-induced obesity, the metabolic profile improvement was linked with dysbiosis correction, strongly supporting the contribution of the GMB in the pathogenesis of OA in these animal models (Rios, 2019; Rios et al., 2019; Schott et al., 2018).

4. Interactions between medications and GMB in OA management.

It is now established that GMB is a critical determinant of drug metabolism and bioavailability, suggesting that specific GMB composition may influence the response to OA medications (Figure 2) (Zhang et al., 2018).

First, medications used to decrease OA symptoms affect GMB. In particular opioids alter GMB composition and many of the significant associations seen between GMB and OA overlap with opioid associations (Banerjee et al., 2016). In addition, NSAID users often take proton pump inhibitors that induce changes of the GMB which may result from the removal

of the low pH barrier between the upper and lower gastro-intestinal tract (Jackson et al., 2016). GMB variation may also influence acetaminophen metabolism and hepatotoxicity (Kim et al., 2018; Li et al., 2016a).

Second, glucosamine sulfate and chondroitin sulfate, two symptomatic slow-acting drugs widely used in OA, have limited intestinal absorption and are predominantly utilized by GMB. They may have prebiotic properties (Rani et al., 2019) and therefore exert their therapeutic effects through gut bacterial pathways. A recent systematic review evaluating the evidence for the effects of glucosamine sulfate and chondroitin sulfate on the GMB, showed that chondroitin sulfate supplementation increases the relative abundance of the gut bacterial genus *Bacteroides*, which may play important roles in regulating the symbiosis in the gut microbial community, as well as host health (Shmagel et al., 2019). The effect of chondroitin sulfate on OA might also be influenced by the composition of the GMB, in particular its pro- or anti-inflammatory activity might depend on the presence of specific commensal probiotic bacterial species. The interactions of chondroitin sulfate with an individual GMB spectrum might lead either to compromise or reinforcement of the colonic mucus barrier, and therefore various patterns of in vivo effects in OA (Wang et al., 2017). For instance, it has been shown that the degradation profile of chondroitin sulfate differs according to various human microbial consortia, which may contribute to unequal efficacy of chondroitin sulfate on OA symptoms among individuals (Shang et al., 2016). Similarly, extracts from green-lipped mussels used as a complementary therapy by patients with OA, modulate the GMB composition, with uncertain clinical benefit on OA symptoms (Coulson et al., 2013; Stebbings et al., 2017). To what extent gut dysbiosis induced by OA medications indirectly increase risk factors of OA such as obesity, metabolic syndrome or loss of muscle mass, remains to be investigated.

Finally, further indirect links might be interesting to consider. An exploratory analysis in the Osteoarthritis Initiative cohort screened 28 medication classes to determine if consistent long-term medication users, compared with nonusers, had different structural and knee pain changes over 24 months. Four medication classes demonstrated a potential signal regarding structural changes, with trends for less disease progression with anti-estrogens, angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, and thyroid agents. Whether these associations are mediated by confounding factors or reflect interactions in metabolic pathways involved in OA pathogenesis remains to be further explored (Driban et al., 2016). It is interesting to note that interactions with the GMB have been reported with metabolic pathways targeted by these commonly used antihypertensive drugs (angiotensin-converting enzyme inhibitors, β-blockers), and with estrogens and thyroid hormones (Baker et al., 2017; Marques et al., 2017; Virili and Centanni, 2017).

5. Research agenda

Although few studies specifically investigated the contribution of GMB to OA, pre-clinical data and observational studies in humans suggest a potential strong relationship between GMB and risk factors, pathogenesis and medications of OA. The role of confounding factors needs to be better explored, in particular genetic background, sex, vitamin D status, age and living conditions, including physical activity, diet composition, as well as concomitant medications. In addition, there are several unanswered issues regarding the potential interaction of GMB and OA. Microbiome composition data in well-characterized OA cohorts are lacking in the absence of stored fecal samples. The links between SCFAs and other microbiota-derived metabolites and OA progression and outcomes need to be investigated in

studies with both radiographic and clinical outcomes. It remains unknown whether serum levels of biomarkers of low-grade inflammation such as LPS or LBP, may be useful to predict OA onset or severity. Finally, randomized controlled studies in humans are required to test whether prebiotic or probiotic supplements, or dietary supplements such as fibers and butyrate, may modify the GMB sufficiently to induce clinically significant and prolonged modifications of OA outcomes (Table 2). This would move the field of OA from symptomatic management to individualized interventions targeting pathogenesis.

Table 1: Interventional studies supporting a contribution of GMB to OA

Study	Setting	Intervention	Control	Duration	Results
Lei et al 2017	Patients with symptomatic knee OA (n=537)	Skimmed milk containing probiotic *Lactobacillus casei* Shirota daily	Skimmed milk containing placebo daily	6 months	- ↓ WOMAC - ↓ VAS scores - ↓ CRP levels
So et al, 2011	MIA-induced OA rat model.	*Lactobacillus casei* ± type II collagen/ glucosamine (CII/Gln)	CII/Gln	10 weeks	Co-administration L. casei + CII/ Gln: - > to *L. casei* or CII/ Gln alone to ↓ pain, cartilage destruction, and lymphocyte infiltration - ↓ expression of inflammatory cytokines and matrix metalloproteinases, and ↑ expression of anti-inflammatory cytokines
Kwon et al, 2018	MIA-induced OA rat model.	Probiotic complex, rosavin, and zinc	Celecoxib or vehicle	Not indicated	- ↓ subchondral bone and cartilage damage - ↓ expression of proinflammatory cytokines and catabolic factors within the joint tissue
Schott et al, 2018	Trauma-induced knee OA (DMM) in a mouse model of high-fat diet–induced obesity and in lean mice.	Prebiotic (oligofructose)	Control fiber (cellulose)	12 weeks	- Greater cartilage and chondrocyte loss in obese versus lean mice of the control group - Complete protection against accelerated OA in obese mice receiving oligofructose - ↓ obesity-induced synovial inflammation - Restoration of the lean gut microbiome in obese mice
Sim et al, 2018	MIA-induced OA rat model.	Butyrate concentrated and lyophilized powder from cultured media of butyric acid-producing probiotic, *Clostridium butyricum* (ID-CBT5101)	Distilled water	6 weeks	- ↓ serum inflammation and bone metabolism markers (*i.e.*, COX-2, IL-6, LTB4 and COMP) - ↑ serum IFN-γ and glycosaminoglycans - ↓ mRNA expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases - Preservation of the knee cartilage and synovial membrane, and ↓ of fibrous tissue
Korotkyi et al, 2019	MIA-induced OA rat model.	Multistrain probiotic for 14 days ± chondroitin sulfate	Chondroitin sulfate	28 days	Cumulative effect of co-administration in knee cartilage : - ↓ mRNA expression pro-inflammatory cytokines - ↑ mRNA expression of collagen type II alpha 1 chain
Rios et al, 2019a 2019b	HFS diet-induced rat model of obesity	Prebiotic fibre supplementation ± HFS diet ± aerobic exercise	Standard chow diet or HFS diet ± aerobic exercise	12 weeks	- Prevention of knee joint damage (Modified Mankin Score) - Associated with a normalization of insulin resistance, leptin levels, dyslipidemia, gut microbiota, and endotoxemia

OA, osteoarthritis: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; VAS, visual analog scale; CRP, C-reactive protein; MIA, Monosodium iodoacetate; DMM, destabilization of the medial meniscus; HFS diet, High-fat/high-sucrose diet.

Table 2: Research priorities to address in the field of GMB and OA management

Research questions	**Outcome**
Associations between GMB or its metabolites and OA in well-characterized and longitudinal cohorts with radiographic and clinical data regarding OA?	- Microbiome composition data - SCFAs and other microbiota-derived metabolites
Role of confounding factors in the associations between GMB and OA?	- Age - Sex - Genetic background - Vitamin D status - Physical activity - Diet composition - Concomitant medications.
Potential predictors of OA onset or severity linked to GMB?	- Biomarkers of low-grade inflammation: LPS, LBP…? - GMB metabolites?
To what extent intervention studies in humans may modify the GMB sufficiently to induce clinically significant and prolonged modifications of OA outcomes?	- Prebiotic or probiotic supplements - Dietary supplements (fibers, butyrate…) - Exercise (various modality and intensity, synergy with different diets…)

GMB, gut microbiota; OA, osteoarthritis; LPS, lipopolysaccharide; LBP, LPS-binding protein.

Figure captions

Figure 1: Interaction between GMB and risk factors of osteoarthritis.

Risk factors of OA can promote OA either directly, or via modulation of GMB. GMB can also be modulated via other environmental or genetic factors which therefore may indirectly impact OA. GMB-independent risk factors also add to the cascade promoting OA.

OA, osteoarthritis; GMB, gut microbiota

Figure 2: Interaction between GMB and drug metabolism and bioavailability in OA.

Potential interactions with GMB have been reported for medications used to decrease OA symptoms, for symptomatic slow-acting drugs used in OA and also for drugs used for non-OA comorbidities.

OA, osteoarthritis; GMB, gut microbiota

Acknowledgements

The meeting was funded by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) under the auspices of the WHO Collaborating Centre for Public Health Aspects of Musculoskeletal Health and Aging.

References

Backhed, F., Ding, H., Wang, T., Hooper, L.V., Koh, G.Y., Nagy, A., Semenkovich, C.F., Gordon, J.I., 2004. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci USA 101, 15718-15723.

Baker, J.M., Al-Nakkash, L., Herbst-Kralovetz, M.M., 2017. Estrogen-gut microbiome axis: Physiological and clinical implications. Maturitas 103, 45-53.

Banerjee, S., Sindberg, G., Wang, F., Meng, J., Sharma, U., Zhang, L., Dauer, P., Chen, C., Dalluge, J., Johnson, T., Roy, S., 2016. Opioid-induced gut microbial disruption and bile dysregulation leads to gut barrier compromise and sustained systemic inflammation. Mucosal Immunol 9, 1418-1428.

Berenbaum, F., 2013. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage 21, 16-21.

Berenbaum, F., 2019. Deep phenotyping of osteoarthritis: a step forward. Ann Rheum Dis 78, 3-5.

Berenbaum, F., Wallace, I.J., Lieberman, D.E., Felson, D.T., 2018. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nat Rev Rheumatol 14, 674-681.

Biagi, E., Nylund, L., Candela, M., Ostan, R., Bucci, L., Pini, E., Nikkila, J., Monti, D., Satokari, R., Franceschi, C., Brigidi, P., De Vos, W., 2010. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. PLoS One 5, e10667.

Biagi, E., Franceschi, C., Rampelli, S., Severgnini, M., Ostan, R., Turroni, S., Consolandi, C., Quercia, S., Scurti, M., Monti, D., Capri, M., Brigidi, P., Candela, M., 2016. Gut Microbiota and Extreme Longevity. Curr Biol 26, 1480-1485.

Bindels, L.B., Neyrinck, A.M., Loumaye, A., Catry, E., Walgrave, H., Cherbuy, C., Leclercq, S., Van Hul, M., Plovier, H., Pachikian, B., Bermudez-Humaran, L.G., Langella, P., Cani, P.D., Thissen, J.P., Delzenne, N.M., 2018. Increased gut permeability in cancer cachexia: mechanisms and clinical relevance. Oncotarget 9, 18224-18238.

Bobacz, K., Sunk, I.G., Hofstaetter, J.G., Amoyo, L., Toma, C.D., Akira, S., Weichhart, T., Saemann, M., Smolen, J.S., 2007. Toll-like receptors and chondrocytes: the lipopolysaccharide-induced decrease in cartilage matrix synthesis is dependent on the presence of toll-like receptor 4 and antagonized by bone morphogenetic protein 7. Arthritis Rheum 56, 1880-1893.

Boutagy, N.E., McMillan, R.P., Frisard, M.I., Hulver, M.W., 2016. Metabolic endotoxemia with obesity: Is it real and is it relevant? Biochimie 124, 11-20.

Calder, P.C., Bosco, N., Bourdet-Sicard, R., Capuron, L., Delzenne, N., Dore, J., Franceschi, C., Lehtinen, M.J., Recker, T., Salvioli, S., Visioli, F., 2017. Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition. Ageing Res Rev 40, 95-119.

Cerda, B., Perez, M., Perez-Santiago, J.D., Tornero-Aguilera, J.F., Gonzalez-Soltero, R., Larrosa, M., 2016. Gut Microbiota Modification: Another Piece in the Puzzle of the Benefits of Physical Exercise in Health? Front Physiol 7, 51.

Claesson, M.J., Cusack, S., O'Sullivan, O., Greene-Diniz, R., de Weerd, H., Flannery, E., Marchesi, J.R., Falush, D., Dinan, T., Fitzgerald, G., Stanton, C., van Sinderen, D., O'Connor, M., Harnedy, N., O'Connor, K., Henry, C., O'Mahony, D., Fitzgerald, A.P., Shanahan, F., Twomey, C., Hill, C., Ross, R.P., O'Toole, P.W., 2011. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. Proc Natl Acad Sci U S A 108 Suppl 1, 4586-4591.

Collins, K.H., Hart, D.A., Reimer, R.A., Seerattan, R.A., Herzog, W., 2016. Response to diet-induced obesity produces time-dependent induction and progression of metabolic osteoarthritis in rat knees. J Orthop Res 34, 1010-1018.

Collins, K.H., Hart, D.A., Seerattan, R.A., Reimer, R.A., Herzog, W., 2018. High-fat/high-sucrose diet-induced obesity results in joint-specific development of osteoarthritis-like degeneration in a rat model. Bone Joint Res 7, 274-281.

Collins, K.H., Paul, H.A., Reimer, R.A., Seerattan, R.A., Hart, D.A., Herzog, W., 2015. Relationship between inflammation, the gut microbiota, and metabolic osteoarthritis development: studies in a rat model. Osteoarthritis Cartilage 23, 1989-1998.

Coulson, S., Butt, H., Vecchio, P., Gramotnev, H., Vitetta, L., 2013. Green-lipped mussel extract (Perna canaliculus) and glucosamine sulphate in patients with knee osteoarthritis: therapeutic efficacy and effects on gastrointestinal microbiota profiles. Inflammopharmacology 21, 79-90.

D'Amelio, P., Sassi, F., 2018. Gut Microbiota, Immune System, and Bone. Calcif Tissue Int 102, 415-425.

Dai, Z., Jafarzadeh, S.R., Niu, J., Felson, D.T., Jacques, P.F., Li, S., Zhang, Y., 2018. Body Mass Index Mediates the Association between Dietary Fiber and Symptomatic Knee Osteoarthritis in the Osteoarthritis Initiative and the Framingham Osteoarthritis Study. J Nutr 148, 1961-1967.

Dai, Z., Lu, N., Niu, J., Felson, D.T., Zhang, Y., 2017a. Dietary Fiber Intake in Relation to Knee Pain Trajectory. Arthritis Care Res (Hoboken) 69, 1331-1339.

Dai, Z., Niu, J., Zhang, Y., Jacques, P., Felson, D.T., 2017b. Dietary intake of fibre and risk of knee osteoarthritis in two US prospective cohorts. Ann Rheum Dis 76, 1411-1419.

de Kruijf, M., Stolk, L., Zillikens, M.C., de Rijke, Y.B., Bierma-Zeinstra, S.M., Hofman, A., Huygen, F.J., Uitterlinden, A.G., van Meurs, J.B., 2016. Lower sex hormone levels are

associated with more chronic musculoskeletal pain in community-dwelling elderly women. Pain 157, 1425-1431.

Driban, J.B., Lo, G.H., Eaton, C.B., Lapane, K.L., Nevitt, M., Harvey, W.F., McCulloch, C.E., McAlindon, T.E., 2016. Exploratory analysis of osteoarthritis progression among medication users: data from the Osteoarthritis Initiative. Ther Adv Musculoskelet Dis 8, 207-219.

Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., Santoro, A., 2018. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol 14, 576-590.

Franceschi, C., Garagnani, P., Vitale, G., Capri, M., Salvioli, S., 2017. Inflammaging and 'Garb-aging'. Trends Endocrinol Metab 28, 199-212.

GBD 2015 DALYs and HALE Collaborators. 2016. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388, 1603-1658.

Gill, R.S., Al-Adra, D.P., Shi, X., Sharma, A.M., Birch, D.W., Karmali, S., 2011. The benefits of bariatric surgery in obese patients with hip and knee osteoarthritis: a systematic review. Obes Rev 12, 1083-1089.

Guss, J.D., Ziemian, S.N., Luna, M., Sandoval, T.N., Holyoak, D.T., Guisado, G.G., Roubert, S., Callahan, R.L., Brito, I.L., van der Meulen, M.C.H., Goldring, S.R., Hernandez, C.J., 2019. The effects of metabolic syndrome, obesity, and the gut microbiome on load-induced osteoarthritis. Osteoarthritis Cartilage 27, 129-139.

Huang, Z., Kraus, V.B., 2016. Does lipopolysaccharide-mediated inflammation have a role in OA? Nat Rev Rheumatol 12, 123-129.

Huang, Z.Y., Perry, E., Huebner, J.L., Katz, B., Li, Y.J., Kraus, V.B., 2018. Biomarkers of inflammation - LBP and TLR- predict progression of knee osteoarthritis in the DOXY clinical trial. Osteoarthritis Cartilage 26, 1658-1665.

Huang, Z.Y., Stabler, T., Pei, F.X., Kraus, V.B., 2016. Both systemic and local lipopolysaccharide (LPS) burden are associated with knee OA severity and inflammation. Osteoarthritis Cartilage 24, 1769-1775.

Hunter, D.J., Bierma-Zeinstra, S., 2019. Osteoarthritis. Lancet 393, 1745-1759.

Iqbal, J., Yuen, T., Sun, L., Zaidi, M., 2016. From the gut to the strut: where inflammation reigns, bone abstains. J Clin Invest 126, 2045-2048.

Jackson, M.A., Goodrich, J.K., Maxan, M.E., Freedberg, D.E., Abrams, J.A., Poole, A.C., Sutter, J.L., Welter, D., Ley, R.E., Bell, J.T., Spector, T.D., Steves, C.J., 2016. Proton pump inhibitors alter the composition of the gut microbiota. Gut 65, 749-756.

Jackson, M.A., Verdi, S., Maxan, M.E., Shin, C.M., Zierer, J., Bowyer, R.C.E., Martin, T., Williams, F.M.K., Menni, C., Bell, J.T., Spector, T.D., Steves, C.J., 2018. Gut microbiota associations with common diseases and prescription medications in a population-based cohort. Nat Commun 9, 2655.

Jang, L.G., Choi, G., Kim, S.W., Kim, B.Y., Lee, S., Park, H., 2019. The combination of sport and sport-specific diet is associated with characteristics of gut microbiota: an observational study. J Int Soc Sports Nutr 16, 21.

Jiang, L., Xie, X., Wang, Y., Wang, Y., Lu, Y., Tian, T., Chu, M., Shen, Y., 2016. Body mass index and hand osteoarthritis susceptibility: an updated meta-analysis. Int J Rheum Dis 19, 1244-1254.

Jin, X., Beguerie, J.R., Zhang, W., Blizzard, L., Otahal, P., Jones, G., Ding, C., 2015. Circulating C reactive protein in osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis 74, 703-710.

Kim, J.K., Choi, M.S., Jeong, J.J., Lim, S.M., Kim, I.S., Yoo, H.H., Kim, D.H., 2018. Effect of Probiotics on Pharmacokinetics of Orally Administered Acetaminophen in Mice. Drug Metab Dispos 46, 122-130.

Korotkyi, O.H., Vovk, A.A., Dranitsina, A.S., Falalyeyeva, T.M., Dvorshchenko, K.O., Fagoonee, S., Ostapchenko, L.I., 2019. The influence of probiotic diet and chondroitin sulfate administration on Ptgs2, Tgfb1 and Col2a1 expression in rat knee cartilage during monoiodoacetate-induced osteoarthritis. Minerva Med. 2019 Apr 1. doi: 10.23736/S0026-4806.19.06063-4

Kwon, J.Y., Lee, S.H., Jhun, J., Choi, J., Jung, K., Cho, K.H., Kim, S.J., Yang, C.W., Park, S.H., Cho, M.L., 2018. The Combination of Probiotic Complex, Rosavin, and Zinc Improves Pain and Cartilage Destruction in an Osteoarthritis Rat Model. J Med Food 21, 364-371.

Lei, M., Guo, C., Wang, D., Zhang, C., Hua, L., 2017. The effect of probiotic Lactobacillus casei Shirota on knee osteoarthritis: a randomised double-blind, placebo-controlled clinical trial. Benef Microbes 8, 697-703.

Li, H., He, J., Jia, W., 2016a. The influence of gut microbiota on drug metabolism and toxicity. Expert Opin Drug Metab Toxicol 12, 31-40.

Li, J.Y., Chassaing, B., Tyagi, A.M., Vaccaro, C., Luo, T., Adams, J., Darby, T.M., Weitzmann, M.N., Mulle, J.G., Gewirtz, A.T., Jones, R.M., Pacifici, R., 2016b. Sex steroid deficiency-associated bone loss is microbiota dependent and prevented by probiotics. J Clin Invest 126, 2049-2063.

Lucas, S., Omata, Y., Hofmann, J., Bottcher, M., Iljazovic, A., Sarter, K., Albrecht, O., Schulz, O., Krishnacoumar, B., Kronke, G., Herrmann, M., Mougiakakos, D., Strowig, T., Schett, G., Zaiss, M.M., 2018. Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. Nat Commun 9, 55.

Mach, N., Fuster-Botella, D., 2017. Endurance exercise and gut microbiota: A review. J Sport Health Sci 6, 179-197.

Mailing, L.J., Allen, J.M., Buford, T.W., Fields, C.J., Woods, J.A., 2019. Exercise and the Gut Microbiome: A Review of the Evidence, Potential Mechanisms, and Implications for Human Health. Exerc Sport Sci Rev 47, 75-85.

Marques, F.Z., Mackay, C.R., Kaye, D.M., 2017. Beyond gut feelings: how the gut microbiota regulates blood pressure. Nature Reviews Cardiology 15, 20.

Mazor, M., Best, T.M., Cesaro, A., Lespessailles, E., Toumi, H., 2019. Osteoarthritis biomarker responses and cartilage adaptation to exercise: A review of animal and human models. Scand J Med Sci Sports. 2019 Apr 29. doi: 10.1111/sms.13435

Metcalfe, D., Harte, A.L., Aletrari, M.O., Al Daghri, N.M., Al Disi, D., Tripathi, G., McTernan, P.G., 2012. Does endotoxaemia contribute to osteoarthritis in obese patients? Clin Sci (Lond) 123, 627-634.

Mills, S., Stanton, C., Lane, J.A., Smith, G.J., Ross, R.P., 2019. Precision Nutrition and the Microbiome, Part I: Current State of the Science. Nutrients 11(4). pii: E923.

Monda, V., Villano, I., Messina, A., Valenzano, A., Esposito, T., Moscatelli, F., Viggiano, A., Cibelli, G., Chieffi, S., Monda, M., Messina, G., 2017. Exercise Modifies the Gut Microbiota with Positive Health Effects. Oxid Med Cell Longev 2017, 3831972.

O'Toole, P.W., Jeffery, I.B., 2015. Gut microbiota and aging. Science 350, 1214-1215.

Quevrain, E., Maubert, M.A., Michon, C., Chain, F., Marquant, R., Tailhades, J., Miquel, S., Carlier, L., Bermudez-Humaran, L.G., Pigneur, B., Lequin, O., Kharrat, P., Thomas, G., Rainteau, D., Aubry, C., Breyner, N., Afonso, C., Lavielle, S., Grill, J.P., Chassaing, G., Chatel, J.M., Trugnan, G., Xavier, R., Langella, P., Sokol, H., Seksik,

P., 2016. Identification of an anti-inflammatory protein from Faecalibacterium prausnitzii, a commensal bacterium deficient in Crohn's disease. Gut 65, 415-425.

Rani, A., Baruah, R., Goyal, A., 2019. Prebiotic Chondroitin Sulfate Disaccharide Isolated from Chicken Keel Bone Exhibiting Anticancer Potential Against Human Colon Cancer Cells. Nutr Cancer 71, 825-839.

Reyes, C., Leyland, K.M., Peat, G., Cooper, C., Arden, N.K., Prieto-Alhambra, D., 2016. Association Between Overweight and Obesity and Risk of Clinically Diagnosed Knee, Hip, and Hand Osteoarthritis: A Population-Based Cohort Study. Arthritis Rheumatol 68, 1869-1875.

Richette, P., Poitou, C., Garnero, P., Vicaut, E., Bouillot, J.L., Lacorte, J.M., Basdevant, A., Clement, K., Bardin, T., Chevalier, X., 2011. Benefits of massive weight loss on symptoms, systemic inflammation and cartilage turnover in obese patients with knee osteoarthritis. Ann Rheum Dis 70, 139-144.

Rios, J.L., 2019. Protective effect of prebiotic and exercise intervention on knee health in a rat model of diet-induced obesity. Cartilage 9, 3893.

Rios, J.L., Bomhof, M.R., Reimer, R.A., Hart, D.A., Collins, K.H., Herzog, W., 2019. Protective effect of prebiotic and exercise intervention on knee health in a rat model of diet-induced obesity. Sci Rep 9, 3893.

Rizzoli, R., 2019. Nutritional influence on bone: role of gut microbiota. Aging Clin Exp Res 31(6):743-751

Robinson, W.H., Lepus, C.M., Wang, Q., Raghu, H., Mao, R., Lindstrom, T.M., Sokolove, J., 2016. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol 12, 580-592.

Russo, R., Cristiano, C., Avagliano, C., De Caro, C., La Rana, G., Raso, G.M., Canani, R.B., Meli, R., Calignano, A., 2018. Gut-brain Axis: Role of Lipids in the Regulation of Inflammation, Pain and CNS Diseases. Curr Med Chem 25, 3930-3952.

Sanna, S., van Zuydam, N.R., Mahajan, A., Kurilshikov, A., Vich Vila, A., Vosa, U., Mujagic, Z., Masclee, A.A.M., Jonkers, D., Oosting, M., Joosten, L.A.B., Netea, M.G., Franke, L., Zhernakova, A., Fu, J., Wijmenga, C., McCarthy, M.I., 2019. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. Nat Genet 51, 600-605.

Santoro, A., Ostan, R., Candela, M., Biagi, E., Brigidi, P., Capri, M., Franceschi, C., 2018. Gut microbiota changes in the extreme decades of human life: a focus on centenarians. Cell Mol Life Sci 75, 129-148.

Schott, E.M., Farnsworth, C.W., Grier, A., Lillis, J.A., Soniwala, S., Dadourian, G.H., Bell, R.D., Doolittle, M.L., Villani, D.A., Awad, H., Ketz, J.P., Kamal, F., Ackert-Bicknell, C., Ashton, J.M., Gill, S.R., Mooney, R.A., Zuscik, M.J., 2018. Targeting the gut microbiome to treat the osteoarthritis of obesity. JCI Insight 3(8). pii: 95997

Sebbag, E., Felten, R., Sagez, F., Sibilia, J., Devilliers, H., Arnaud, L., 2019. The world-wide burden of musculoskeletal diseases: a systematic analysis of the World Health Organization Burden of Diseases Database. Ann Rheum Dis 78, 844-848.

Shang, Q., Yin, Y., Zhu, L., Li, G., Yu, G., Wang, X., 2016. Degradation of chondroitin sulfate by the gut microbiota of Chinese individuals. Mediators Inflamm 86, 112-118.

Shmagel, A., Demmer, R., Knights, D., Butler, M., Langsetmo, L., Lane, N.E., Ensrud, K., 2019. The Effects of Glucosamine and Chondroitin Sulfate on Gut Microbial Composition: A Systematic Review of Evidence from Animal and Human Studies. Nutrients 11(2). pii: E294

Sim, B.Y., Choi, H.J., Kim, M.G., Jeong, D.G., Lee, D.G., Yoon, J.M., Kang, D.J., Park, S., Ji, J.G., Joo, I.H., Kim, D.H., 2018. Effects of ID-CBT5101 in Preventing and Alleviating Osteoarthritis Symptoms in a Monosodium Iodoacetate-Induced Rat Model. J Microbiol Biotechnol 28, 1199-1208.

So, J.S., Song, M.K., Kwon, H.K., Lee, C.G., Chae, C.S., Sahoo, A., Jash, A., Lee, S.H., Park, Z.Y., Im, S.H., 2011. Lactobacillus casei enhances type II collagen/glucosamine-mediated suppression of inflammatory responses in experimental osteoarthritis. Life Sci 88, 358-366.

Sokol, H., Pigneur, B., Watterlot, L., Lakhdari, O., Bermudez-Humaran, L.G., Gratadoux, J.J., Blugeon, S., Bridonneau, C., Furet, J.P., Corthier, G., Grangette, C., Vasquez, N., Pochart, P., Trugnan, G., Thomas, G., Blottiere, H.M., Dore, J., Marteau, P., Seksik, P., Langella, P., 2008. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A 105, 16731-16736.

Srikanth, V.K., Fryer, J.L., Zhai, G., Winzenberg, T.M., Hosmer, D., Jones, G., 2005. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage 13, 769-781.

Stebbings, S., Gray, A., Schneiders, A.G., Sansom, A., 2017. A randomized double-blind placebo-controlled trial to investigate the effectiveness and safety of a novel green-lipped mussel extract -BioLex(R) -for managing pain in moderate to severe osteoarthritis of the hip and knee. BMC Complement Altern Med 17, 416.

Steves, C.J., Bird, S., Williams, F.M., Spector, T.D., 2016. The Microbiome and Musculoskeletal Conditions of Aging: A Review of Evidence for Impact and Potential Therapeutics. J Bone Miner Res 31, 261-269.

Szychlinska, M.A., Di Rosa, M., Castorina, A., Mobasheri, A., Musumeci, G., 2019. A correlation between intestinal microbiota dysbiosis and osteoarthritis. Heliyon 5, e01134.

Ulici, V., Kelley, K.L., Azcarate-Peril, M.A., Cleveland, R.J., Sartor, R.B., Schwartz, T.A., Loeser, R.F., 2018. Osteoarthritis induced by destabilization of the medial meniscus is reduced in germ-free mice. Osteoarthritis Cartilage 26, 1098-1109.

Veronese, N., Koyanagi, A., Stubbs, B., Cooper, C., Guglielmi, G., Rizzoli, R., Punzi, L., Rogoli, D., Caruso, M.G., Rotolo, O., Notarnicola, M., Al-Daghri, N., Smith, L., Reginster, J.Y., Maggi, S., 2018. Mediterranean diet and knee osteoarthritis outcomes: A longitudinal cohort study. Clin Nutr. 2018 Dec 4. pii: S0261-5614(18)32565-2. doi: 10.1016/j.clnu.2018.11.032

Virili, C., Centanni, M., 2017. "With a little help from my friends" - The role of microbiota in thyroid hormone metabolism and enterohepatic recycling. Mol Cell Endocrinol 458, 39-43.

Visser, A.W., de Mutsert, R., le Cessie, S., den Heijer, M., Rosendaal, F.R., Kloppenburg, M., 2015. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. Ann Rheum Dis 74, 1842-1847.

Wallace, I.J., Worthington, S., Felson, D.T., Jurmain, R.D., Wren, K.T., Maijanen, H., Woods, R.J., Lieberman, D.E., 2017. Knee osteoarthritis has doubled in prevalence since the mid-20th century. Proc Natl Acad Sci U S A 114, 9332-9336.

Wang, F., Yu, T., Huang, G., Cai, D., Liang, X., Su, H., Zhu, Z., Li, D., Yang, Y., Shen, P., Mao, R., Yu, L., Zhao, M., Li, Q., 2015. Gut Microbiota Community and Its Assembly Associated with Age and Diet in Chinese Centenarians. J Microbiol Biotechnol 25, 1195-1204.

Wang, Q., Huang, S.Q., Li, C.Q., Xu, Q., Zeng, Q.P., 2017. Akkermansia muciniphila May Determine Chondroitin Sulfate Ameliorating or Aggravating Osteoarthritis. Front Microbiol 8, 1955.

Wang, Y., Kuang, Z., Yu, X., Ruhn, K.A., Kubo, M., Hooper, L.V., 2017. The intestinal microbiota regulates body composition through NFIL3 and the circadian clock. Science 357, 912-916.

Yusuf, E., Nelissen, R.G., Ioan-Facsinay, A., Stojanovic-Susulic, V., DeGroot, J., van Osch, G., Middeldorp, S., Huizinga, T.W., Kloppenburg, M., 2010. Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis 69, 761-765.

Zhang, J., Zhang, J., Wang, R., 2018. Gut microbiota modulates drug pharmacokinetics. Drug Metab Rev 50, 357-368.

Zhao, Y., Chen, B., Li, S., Yang, L., Zhu, D., Wang, Y., Wang, H., Wang, T., Shi, B., Gai, Z., Yang, J., Heng, X., Yang, J., Zhang, L., 2018. Detection and characterization of bacterial nucleic acids in culture-negative synovial tissue and fluid samples from rheumatoid arthritis or osteoarthritis patients. Sci Rep 8, 14305.